(FILE 'HOME' ENTERED AT 17:07:03 ON 12 DEC 2003)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, EMBASE, BIOSIS, CAPLUS' ENTERED AT 17:07:21 ON 12 DEC 2003

L1 23 S DODMA

L2 13 DUP REM L1 (10 DUPLICATES REMOVED)

=>

WEST

# Freeform Search

**Database:**
- US Patents Full-Text Database
- US Pre-Grant Publication Full-Text Database
- JPO Abstracts Database
- EPO Abstracts Database
- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

**Term:**

**Display:** 10 **Documents in Display Format:** CIT **Starting with Number** 1

**Generate:** ○ **Hit List** ◉ **Hit Count** ○ **Side by Side** ○ **Image**

Search | Clear | Help | Logout | Interrupt

Main Menu | Show S Numbers | Edit S Numbers | Preferences | Cases

## Search History

**DATE: Friday, December 12, 2003** Printable Copy Create Case

| Set Name side by side | Query | Hit Count | Set Name result set |
|---|---|---|---|
| *DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ* | | | |
| L14 | L13 and l12 | 1 | L14 |
| L13 | protein or polypeptide | 375006 | L13 |
| L12 | 6207646.pn. | 2 | L12 |
| L11 | l2 and l10 | 0 | L11 |
| L10 | 5705385.pn. | 2 | L10 |
| L9 | l7 and l8 | 0 | L9 |
| L8 | 5703385.pn. | 2 | L8 |
| L7 | DODMA | 17 | L7 |
| *DB=USPT; PLUR=YES; OP=ADJ* | | | |
| L6 | N,N-dimethyl-2,3-dioleyloxy propylamine | 1 | L6 |
| L5 | 1,2-dioleyl-3-N,N-dimethylamino propane | 1 | L5 |
| L4 | encapsulated and l2 | 4 | L4 |
| L3 | L2 and l1 | 0 | L3 |
| L2 | DODMA | 8 | L2 |
| L1 | 5703055.pn. | 1 | L1 |

END OF SEARCH HISTORY

WEST

**End of Result Set**

Generate Collection | Print

L10: Entry 2 of 2 File: DWPI Dec 19, 1996

DERWENT-ACC-NO: 1997-065193
DERWENT-WEEK: 200367


TITLE: Charge-neutralised complex of cationic lipid and nucleic acid soluble in organic solvent - and derived particles, for delivering nucleic acid to cells for in vivo or in vitro gene transfer, are stable in serum and protected against degradation

PRIORITY-DATA: 1995US-0485458 (June 7, 1995), 1995US-0484282 (June 7, 1995), 2000AU-0071667 (November 17, 2000), 1999US-0436933 (November 8, 1999), 2003US-0374673 (February 24, 2003)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|---|---|---|---|---|
| WO 9640964 A2 | December 19, 1996 | E | 119 | C12N015/88 |
| AU 9663307 A | December 30, 1996 | | 000 | C12N015/88 |
| WO 9640964 A3 | April 24, 1997 | | 000 | C12N015/88 |
| US 5705385 A | January 6, 1998 | | 023 | C12N015/85 |
| EP 832271 A2 | April 1, 1998 | E | 000 | C12N015/88 |
| JP 11507537 W | July 6, 1999 | | 141 | C12N015/09 |
| AU 723163 B | August 17, 2000 | | 000 | C12N015/88 |
| AU 200071667 A | February 8, 2001 | | 000 | C12N015/88 |
| US 6534484 B1 | March 18, 2003 | | 000 | A01N043/04 |
| US 20030181410 A1 | September 25, 2003 | | 000 | A61K031/70 |

APPLICATION-DATA:

| PUB-NO | APPL-DATE | APPL-NO | DESCRIPTOR |
|---|---|---|---|
| WO 9640964A2 | June 6, 1996 | 1996WO-US09949 | |
| AU 9663307A | June 6, 1996 | 1996AU-0063307 | |
| AU 9663307A | | WO 9640964 | Based on |
| WO 9640964A3 | June 6, 1996 | 1996WO-US09949 | |
| US 5705385A | June 7, 1995 | 1995US-0485458 | |
| EP 832271A2 | June 6, 1996 | 1996EP-0922432 | |
| EP 832271A2 | June 6, 1996 | 1996WO-US09949 | |
| EP 832271A2 | | WO 9640964 | Based on |
| JP 11507537W | June 6, 1996 | 1996WO-US09949 | |
| JP 11507537W | June 6, 1996 | 1997JP-0502106 | |
| JP 11507537W | | WO 9640964 | Based on |
| AU 723163B | June 6, 1996 | 1996AU-0063307 | |
| AU 723163B | | AU 9663307 | Previous Publ. |
| AU 723163B | | WO 9640964 | Based on |
| AU 200071667A | June 6, 1996 | 1996AU-0063307 | Div ex |
| AU 200071667A | November 17, 2000 | 2000AU-0071667 | |
| AU 200071667A | | AU 723163 | Div ex |
| US 6534484B1 | June 7, 1995 | 1995US-0484282 | Cont of |
| US 6534484B1 | November 8, 1999 | 1999US-0436933 | |
| US 6534484B1 | | US 5981501 | Cont of |
| US20030181410A1 | June 7, 1995 | 1995US-0484282 | Cont of |
| US20030181410A1 | November 8, 1999 | 1999US-0436933 | Cont of |
| US20030181410A1 | February 24, 2003 | 2003US-0374673 | |
| US20030181410A1 | | US 5981501 | Cont of |
| US20030181410A1 | | US 6534484 | Cont of |

INT-CL (IPC): A01 N 43/04; A61 K 9/127; A61 K 31/70; A61 K 48/00; C12 N 15/09; C12 N 15/85; C12 N 15/88

WEST

Generate Collection | Print

L4: Entry 3 of 4 File: USPT Sep 11, 2001

US-PAT-NO: 6287591
DOCUMENT-IDENTIFIER: US 6287591 B1

TITLE: Charged therapeutic agents encapsulated in lipid particles containing four lipid components

DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 424/450; 428/402.2, 435/177, 435/458, 514/44, 536/22.1

APPL-NO: 09/ 078954 [PALM]
DATE FILED: May 14, 1998

PARENT-CASE:
This application is a continuation-in-part of U.S. patent application Ser. No. 08/856,374 filed May 14, 1997, now abandoned, which is incorporated herein by reference.

WEST

Generate Collection | Print

L4: Entry 3 of 4 File: USPT Sep 11, 2001

US-PAT-NO: 6287591
DOCUMENT-IDENTIFIER: US 6287591 B1

TITLE: Charged therapeutic agents encapsulated in lipid particles containing four lipid components

DATE-ISSUED: September 11, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---|---|---|---|---|
| Semple; Sean C. | Vancouver | | | CA |
| Klimuk; Sandra K. | N. Vancouver | | | CA |
| Harasym; Troy | Vancouver | | | CA |
| Hope; Michael J. | Vancouver | | | CA |
| Ansell; Steven M. | Vancouver | | | CA |
| Cullis; Pieter | Vancouver | | | CA |
| Scherrer; Peter | Vancouver | | | CA |
| Debeyer; Dan | Vancouver | | | CA |

US-CL-CURRENT: 424/450; 428/402.2, 435/177, 435/458, 514/44, 536/22.1

CLAIMS:

What is claimed is:

1. A composition comprising lipid-therapeutic agent particles comprising a lipid portion and a charged therapeutic agent, said charged therapeutic agent being encapsulated in said lipid portion, wherein said lipid portion comprises a first lipid component, a second lipid component, a third lipid component, and a fourth lipid component, said first lipid component being selected from among lipids containing a protonatable or deprotonatable group that has a pKa such that the lipid is in a charged form at a first pH and a neutral form at a second pH, wherein the pKa of the first lipid component is in the range of from 4 to 11, and said first lipid component being further selected such that the charged form is cationic when the therapeutic agent is anionic and anionic when the therapeutic agent is cationic, said second lipid component being selected from among lipids that prevent particle aggregation during lipid-therapeutic agent particle formation and which exchange out of the lipid particle at a rate greater than PEG-CerC20, said third lipid component being a neutral lipid selected from the group consisting of DSPC, POPC, DOPE, and SM, and said fourth lipid component being Chol.

2. The composition according to claim 1, wherein at least some of the protonatable or deprotonatable groups are disposed on the exterior surface, of the particles and at least some of these groups have been neutralized.

3. The composition according to claim 2, wherein the therapeutic agent is anionic.

4. The composition according to claim 3, wherein the therapeutic agent is a polyanionic nucleic acid.

5. The composition according to claim 4, wherein the polyanionic nucleic acid is an antisense nucleic acid.

6. The composition according to claim 4, wherein at least 50% of the polyanionic nucleic acid in the composition is encapsulated within the particle.

7. The composition of claim 4, wherein at least 90% of the polyanionic nucleic acid in the composition is encapsulated within the particle.

8. The composition of claim 4, wherein the polyanionic nucleic acid has exclusively phosphodiester linkages.

9. The composition of according to claim 3, wherein the first lipid component is an amino lipid.

10. The composition of claim 9, wherein the second lipid component is a polyethylene glycol-modified or polyamide oligomer-modified lipid.

11. The composition of claim 3, wherein the second lipid component is a polyethylene glycol-modified or polyamide oligomer-modified lipid.

12. A composition comprising lipid-therapeutic agent particles comprising a lipid portion and a charged therapeutic agent, said charged therapeutic agent being encapsulated in said lipid portion, wherein said lipid portion comprises a first lipid component, a second lipid component, a third lipid component and a fourth lipid component, said first lipid component being selected from among lipids containing a protonatable group that has a pKa such that the lipid is in a charged form at a first pH and a neutral form at a second pH, and said second lipid component being selected from among lipids that prevent particle aggregation during lipid-nucleic acid particle formation, said third lipid component being a neutral lipid selected from the group consisting of DSPC, POPC, DOPE, and SM, and said fourth lipid component being Chol, said particles having a nucleic acid/lipid ratio of at least 10% by weight and a size of from about 70 to about 200 nm, wherein said therapeutic agent is a polyanionic nucleic acid, said nucleic acid having exclusively phophodiester linkages, and wherein at least some of said protonatable groups are disposed on the exterior surface of the particles and at least some of these groups have been neutralized.

13. The composition according to claim 12, wherein the nucleic acid is an antisense nucleic acid.

14. The composition of according to claim 12, wherein the first lipid component is an amino lipid.

15. The composition of claim 14, wherein the second lipid component is a polyethylene glycol-modified lipid.

16. The composition of claim 12, wherein the second lipid component is a polyethylene glycol-modified lipid.

17. The composition of claim 12, wherein the first lipid component is an amino lipid, and the second component is PEG-modified or polyamide oligomer-modified lipid, and wherein said lipids are present at molar percents of about 25-45% neutral lipid, about 35-55% cholesterol, about 10-40% amino lipid and about 0.5-15% PEG-modified or Polyamide oligomer-modified lipid.

18. The composition of claim 12, wherein said lipid portion comprises DODAP as the first lipid component, DSPC as the neutral lipid, and PEG-CerC14 as the second lipid component.

19. The composition of claim 18, wherein the lipid components are present in molar percents of about 25-45% DSPC, about 35-55% Chol, about 10-40% DODAP and about 0.5-15% PEG-CerC14.

20. The composition of claim 12, wherein said lipid portion comprises DODAP, POPC, Chol and PEG-CerC14.

21. The composition of claim 12, wherein said lipid comprises of DODAP, SM, Chol and PEG-CerC14.

22. The composition according to claim 12, wherein at least 50% of the nucleic acid in the composition is encapsulated within the particle.

23. The composition of claim 12, wherein at least 90% of the nucleic acid in the composition is encapsulated within the particle.

24. The composition of claim 12, wherein said nucleic acid is a ribozyme.

25. The composition of claim 14, wherein the second lipid component is a polyethylene glycol-modified or polyamide oligomer-modified lipid.

26. The composition of claim 12, wherein the second lipid component is a polyethylene glycol-modified or polyamide oligomer-modified lipid.

27. A method for preparation of a composition comprising lipid-encapsulated therapeutic agent particles, said method comprising the steps of:

(a) preparing a mixture of lipids comprising a first lipid component, a second lipid component, a third lipid component, and a fourth lipid component, and combining the mixture of lipids with a buffered aqueous solution of a charged therapeutic agent to form an intermediate mixture containing lipid-encapsulated therapeutic agent particles having exterior surface charges, wherein said first lipid component is selected from among lipids containing a protonatable or deprotonatable group that has a pKa such that the lipid is in a charged form at a first pH and a neutral form at a second pH, wherein the pKa of the first lipid component is in the range of from 4 to 11, said buffered solution having a pH such that the first lipid component is in its charged form when in the buffered solution, said first lipid component being further selected such that the charged form is cationic when the charged therapeutic agent is anionic in the buffered solution, and anionic when the charged therapeutic agent is cationic in the buffered solution, and said second lipid component being selected from among lipids that prevent particle aggregation during lipid-therapeutic agent particle formation, said third lipid component being a neutral lipid selected from the group consisting of DSPC, POPC, DOPE, and SM, and said fourth lipid component being Chol, and

(b) changing the pH of the intermediate mixture to neutralize at least some of the exterior surface charges on said lipid-encapsulated therapeutic agent particles to provide at least partially-surface neutralized lipid-encapsulated therapeutic agent particles.

28. The method of claim 27, wherein said composition consists essentially of lipid-nucleic acid particles, said particles having a size of from 70 nm to about 200 nm.

29. The method of claim 27, wherein said mixture of lipids in step (a) is a mixture of lipids in alcohol.

30. The method of claim 27, wherein the first lipid component is an amino lipid.

31. The method of claim 27, wherein the second lipid component is a polyethylene glycol-modified or polyamide oligomer-modified lipid.

32. The method of claim 31, wherein the second lipid component is a PEG-Ceramide.

33. The method of claim 31, wherein the first lipid component is an amino lipid.

34. The method of claim 27, wherein said lipid mixture comprises an amino lipid having a pKa of from about 5 to about 11 as the first lipid component, and a

PEG-modified or Polyamide oligomer-modified lipid as the second component.

35. The method of claim 34, wherein said lipid mixture comprises in molar percents about 25-45% neutral lipid, about 35-55% Chol, about 10-40% amino lipid and about 0.5-15% PEG-Ceramide as the modified lipid.

36. The method of claim 27, wherein said mixture of lipids comprises DODAP as the first lipid component, DSPC as the neutral lipid, and PEG-CerC14 as the second lipid component.

37. The method of claim 36, wherein said lipids are present in molar percents of about 25-45% DSPC, about 35-55% Chol, about 10-40% DODAP and about 0.5-15% PEG-CerC14.

38. The method of claim 27, wherein said mixture of lipids comprises DODAP as the first lipid component, POPC as the neutral lipid, and PEG-CerC14 as the second lipid component.

39. The method of claim 27, wherein said mixture of lipids comprises DODAP as the first lipid component, SM as the neutral lipid, and PEG-CerC14 as the second lipid component.

40. The method of claim 27, wherein the pH is changed in step (b) to physiological pH.

41. The method of claim 27, wherein the step of changing the pH is performed using tangential flow dialysis.

42. A pharmaceutical composition comprising lipid-encapsulated therapeutic agent particles prepared according to claim 27 and a pharmaceutically acceptable carrier.

43. The method of claim 27, wherein the therapeutic agent is a polyanionic nucleic acid.

44. A pharmaceutical composition comprising lipid-encapsulated therapeutic agent particles comprising a polyanionic nucleic acid as therapeutic agent prepared according to claim 43 and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition according to claim 44, wherein the polyanionic nucleic acid is an antisense nucleic acid.

46. A method for preparation of a composition comprising lipid encapsulated therapeutic agent particles, said method comprising the steps of:

(a) preparing a mixture of lipids comprising an amino lipid, a neutral lipid, a sterol, and a PEG-modified or polyamide oligomer-modified lipid, and combining the mixture of lipids with a buffered aqueous solution of a charged therapeutic agent to form an intermediate mixture containing lipid-encapsulated therapeutic agent particles having exterior surface charges, wherein the amino lipid is selected from among lipids containing a protonatable or deprotonatable group that has a pKa such that the amino lipid is in a charged form at a first pH and a neutral form at a second pH, and said buffered solution having a pH such that the amino lipid is in its charged form when in the buffered solution, said amino lipid being further selected such that the charged form is cationic, said PEG-modified or polyamide oligomer-modified lipid being selected from among lipids that prevent particle aggregation during lipid-nucleic acid particle formation, said neutral lipid being selected from the group consisting of DSPC, POPC, DOPE, and SM, and said sterol being Chol, and said therapeutic agent being a polyanionic nucleic acid, and

(b) changing the pH of the intermediate mixture to neutralize at least some of the exterior surface charges on said lipid-encapsulated therapeutic agent particles to provide at least partially-surface neutralized lipid-encapsulated therapeutic agent particles.

47. The method of claim 46, wherein said composition consists essentially of lipid-nucleic acid particles, said particles having a size of from 70 nm to about 200 nm.

48. The method of claim 46, wherein said mixture of lipids in step (a) is a mixture of lipids in alcohol.

49. The method of claim 46, wherein the second lipid component is a PEG-Ceramide.

50. The method of claim 46, wherein said lipids are present in molar percents of about 25-45% neutral lipid, 35-55% Chol, 10-40% amino lipid and 0.5-15% PEG-modified or polyamide oligomer-modified lipid.

51. The method of claim 46, wherein said mixture of lipids comprises DODAP as the amino lipid, DSPC as the neutral lipid, and PEG-CerC14 as the PEG-modified lipid.

52. The method of claim 51, wherein said lipids are present in molar percents of about 25-45% DSPC, about 35-55% Chol, about 10-40% DODAP and about 0.5-15% PEG-CerC14.

53. The method of claim 46, wherein said mixture of lipids comprises DODAP as the amino lipid, POPC as the neutral lipid, and PEG-CerC14 as the PEG-modified lipid.

54. The method of claim 46, wherein said mixture of lipids comprises DODAP as the amino lipid, SM as the neutral lipid, and PEG-CerC14 as the PEG-modified lipid.

55. The method of claim 46, wherein said polyanionic nucleic acid is an antisense nucleic acid.

56. The method of claim 55, wherein said antisense nucleic acid contains linkages selected from the group consisting of phosphodiester, phosphorothioate, phosphorodithioate, boranophosphate, phosphoroselenate and amidate linkages.

57. The method of claim 46, wherein said polyanionic nucleic acid contains exclusively phosphodiester linkages.

58. The method of claim 57, wherein said polyanionic nucleic acid is an antisense nucleic acid.

59. The method of claim 57, wherein the buffered solution comprises 10 to 50 mM citrate or phosphate buffer.

60. The method of claim 46, wherein the polyanionic nucleic acid contains at least some phosphorothioate or phosphorodithioate linkages.

61. The method of claim 60, wherein the buffered solution comprises 10 to 300 mM citrate or phosphate buffer.

62. The method of claim 46, wherein said polyanionic nucleic acid is a ribozyme.

63. A method for introducing a polyanionic nucleic acid into a cell, comprising contacting a cell with a composition containing the polyanionic nucleic acid for a period of time sufficient to introduce the polyanionic nucleic acid into said cell, wherein the composition comprises lipid-encapsulated therapeutic agent particles containing the polyanionic nucleic acid and said composition is prepared according to the method of claim 46.

64. A method for the treatment or prevention of a disease characterized by aberrant expression of a gene in a mammalian subject comprising,

preparing a lipid-encapsulated therapeutic agent particle, wherein the therapeutic agent is a polyanionic nucleic acid, according to the method of claim 46, wherein the polyanionic nucleic acid hybridizes specifically with the aberrantly expressed gene; and

administering a therapeutically effective or prophylactic amount of the particle to the mammalian subject, whereby expression of the aberrantly expressed gene is reduced.

65. The method of claim 64, wherein the gene is selected from among ICAM-1, c-myc, c-myb, ras, raf, erb-B-2, PKC-alpha, IGF-1R, EGFR, VEGF and VEGF-R-1.

66. The method of claim 64, wherein the disease is a tumor.

67. The method of claim 64, wherein the disease is characterized by inflammation.

68. The method of claim 64, wherein the disease is an infectious disease.

69. The method of claim 64, wherein the therapeutically effective amount of the particle is administered to the mammalian subject by intravenous injection.

70. The method of claim 69, wherein the therapeutically effective amount of the particle is administered to the mammalian subject by intravenous injection at an injection site, and wherein the disease is localized at a disease site distal to the injection site.

71. The method of claim 64, wherein the polyanionic nucleic acid comprises exclusively phosphodiester linkages.

72. A method of preventing expression of a disease-associated gene in a mammalian cell comprising,

preparing a lipid-encapsulated therapeutic agent particle, wherein the therapeutic agent is an antisense polyanionic nucleic acid, according to the method of claim 55; and

exposing the mammalian cell to the lipid-encapsulated therapeutic agent particle for a period of time sufficient for the therapeutic agent to enter the cell;

wherein the therapeutic agent has a sequence complementary to the disease-associated gene and reduces the production of the gene product of the disease-associated gene in the cell.

WEST

**End of Result Set**

Generate Collection | Print

L4: Entry 4 of 4 File: USPT Nov 2, 1999

US-PAT-NO: 5976567
DOCUMENT-IDENTIFIER: US 5976567 A

TITLE: Lipid-nucleic acid particles prepared via a hydrophobic lipid-nucleic acid complex intermediate and use for gene transfer

DATE-ISSUED: November 2, 1999

US-CL-CURRENT: 424/450; 435/458, 514/44

APPL-NO: 08/ 660025 [PALM]
DATE FILED: June 6, 1996

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/485,458, filed Jun. 7, 1995, and of U.S. application Ser. No. 08/484,282, filed on Jun. 7, 1995, now U.S. Pat. No. 5,705,385.

WEST

Generate Collection | Print

L7: Entry 16 of 17 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5976567 A
TITLE: Lipid-nucleic acid particles prepared via a hydrophobic lipid-nucleic acid complex intermediate and use for gene transfer

Detailed Description Text (316):
This example illustrates the encapsulation of plasmid DNA in a lipid vesicles by the detergent dialysis method using different cationic lipids. The dialysis method is as described previously for DODAC (EXAMPLE 1). The amount of plasmid entrapped with different mol % of the various cationic lipids was determined by DEAE Sepharose chromatography (described in EXAMPLE 2). The entrapment efficiency was similar for all cationic lipids tested with approximately 50 to 60% of plasmid DNA. The cationic lipid concentration required in the formulation for optimal plasmid encapsulation was 6.5 % for DOTMA, DSDAC and DODMA-AN in FIG. 41(a); 8% DODAC and DMRIE in 41(b); DCchol in 41(c).